Osteoarthritis and Cartilage 28 (2020) 1220–1228

Osteoarthritis and Cartilage

Brief Report

Association of knee OA structural phenotypes to risk for progression: a secondary analysis from the Foundation for National Institutes of Health Osteoarthritis Biomarkers study (FNIH)

F.W. Roemer † ‡ *, J.E. Collins §, T. Neogi ||, M.D. Crema † ¶, A. Guermazi † #

† *Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, 820 Harrison Avenue, FGH Building, 4th floor, Boston, MA, 02118, USA*
‡ *Department of Radiology, Friedrich-Alexander University Erlangen-Nürnberg (FAU) and Universitätsklinikum Erlangen, Maximiliansplatz 3, 91054, Erlangen, Germany*
§ *Orthopaedics and Arthritis Center of Outcomes Research, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, BTM Suite 5016, Boston, MA, 02115, USA*
|| *Boston University School of Medicine, Department of Medicine, Section of Rheumatology, 650 Albany Street, Suite X-20, Boston, MA, 02118, USA*
¶ *Institute of Sports Imaging, French National Institute of Sports (INSEP), 11 Avenue du Tremblay, 75012, Paris, France*
# *Department of Radiology, VA Boston Healthcare System, 1400 VFW Parkway, Suite 1B105, West Roxbury, MA, 02132, USA*

ARTICLE INFO

Article history:
Received 4 February 2020
Accepted 6 May 2020

Keywords:
MRI
Osteoarthritis
Eligibility
Clinical trial

SUMMARY

Purpose: Aim was to stratify the knee MRIs of the Foundation for National Institutes of Health Osteoarthritis Biomarkers Consortium (FNIH) cohort into distinct structural phenotypes based on semi-quantitative assessment and to determine risk for pain and structural progression over 48 months.
Methods: The study sample from the FNIH project was selected as a nested case–control study with knees showing either 1) radiographic and pain progression (i.e., "composite" cases), 2) radiographic progression only ("JSL"), 3) pain progression only, and 4) neither radiographic nor pain progression. MRI was performed on 3T systems. MRIs were read according to the MOAKS scoring system. Knees were stratified into subchondral bone, cartilage/meniscus and inflammatory phenotypes using the baseline visits. The relation of each phenotype to risk of being in the combined JSL plus composite outcome or composite case only group compared to those not having that phenotype was determined using logistic regression. Only KL2 and 3 and those without root tears were included.
Results: 485 knees were included. 362 (75%) did not have any phenotype, while 95 (20%) had the bone phenotype, 22 (5%) the cartilage/meniscus phenotype and 19 (4%) the inflammatory phenotype. The bone phenotype was associated with a higher odds of the combined JSL plus composite outcome and composite outcome only (OR 1.81; [95%CI 1.14,2.85] and 1.65; 95%CI [1.04,2.61]) while the inflammatory (OR 0.96 [95%CI 0.38,2.42] and 1.25; 95%CI [0.48,3.25]) and the cartilage/meniscus phenotypes were not significantly associated with outcome (OR 1.30 95%CI [0.55,3.07] and 0.99; 95%CI [0.40,2,49]).
Conclusions: The bone phenotype was associated with increased risk of having both radiographic and pain progression. Phenotypic stratification may be useful to consider when selecting patients for inclusion in clinical trials.

Introduction

Imaging plays an important role in defining structural disease severity and potential suitability of patients recruited to disease-modifying osteoarthritis drug (DMOAD) trials. From a structural perspective, it is knees with Kellgren–Lawrence (K-L) grades 2 and 3 that are commonly considered eligible for inclusion[1]. Acknowledging the heterogeneity of knee OA, several phenotypes or

* Address correspondence and reprint requests to: F.W. Roemer, Department of Radiology, University of Erlangen-Nuremberg, Maximiliansplatz 3, 91054, Erlangen, Germany. Tel: 49-9131-8536065; fax: 49-9131-8536068.
E-mail addresses: frank.roemer@uk-erlangen.de, froemer@bu.edu (F.W. Roemer).

https://doi.org/10.1016/j.joca.2020.05.008
1063-4584/

subpopulations in OA that are characterized by distinct clinical manifestations of disease have been suggested, based on certain laboratory parameters, biochemical markers, and/or imaging findings[2]. While magnetic resonance imaging (MRI)-based phenotypic characterization of large cohort or clinical trial data is not available to date, three main structural phenotypes in knee OA have been proposed, i.e., inflammation, cartilage/meniscus and subchondral bone[3]. These may progress differently and may represent distinct tissue targets for DMOAD approaches.

Recently, Rapid OsteoArthritis MRI Eligibility Score (ROAMES) system has been introduced that allows phenotypic stratification based on abbreviated MRI assessment and thus, may potentially be applicable in screening efforts for inclusion into clinical DMOAD trials[4]. However, phenotypic stratification will be particularly relevant if rates of structural or clinical progression differ between those showing a distinct structural phenotype vs those who do not exhibit that phenotype[5].

Our aim was to stratify the Foundation for National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium cohort, a well-defined subsample of the larger Osteoarthritis Initiative (OAI) study comparable to a clinical trial population, into distinct structural phenotypes based on semiquantitative MRI assessment at baseline and to determine their risk for structural progression only and both, structural and pain progression combined over 48 months.

Methods

Sample selection

The FNIH Osteoarthritis Biomarkers Consortium study is a nested case–control study embedded within the larger OAI study[6]. In brief, the OAI is a multicenter prospective observational cohort study of knee OA (https://oai.nih.gov) that enrolled 4,796 participants aged 45–79 years at four clinical centers. Details of the OAI inclusionary and exclusionary criteria have been published[7].

Case-control selection

For the nested case–control study, a predetermined number of index knees was selected in the following outcome groups: 1) case knees had both radiographic and pain progression (i.e., "composite cases"); control knees did not have this combination, and included 2) knees with radiographic but not pain progression (joint space loss - "JSL-group"), 3) knees with pain progression but not radiographic progression, and 4) knees with neither radiographic nor pain progression. Radiographic progression was defined by a decrease in minimal joint space width of $\geq$0.7 mm in the medial tibio-femoral compartment from baseline to 24, 36 or 48 months. Knee pain was assessed using the Western Ontario McMasters (WOMAC) pain subscale. Symptomatic progression was defined as a persistent ($\geq$2 time points) increase of $\geq$9 points on a 0–100 normalized WOMAC score from baseline to 24, 36, 48 or 60 months. This difference has been documented to be clinically relevant[8]. The sample size for cases and these three control groups was 194, 103, 103 and 200 knees, respectively[6]. Knees were frequency matched on baseline BMI category and KL Grade. The specifics of the subject selection have been described in detail and are available at: https://oai.epi-ucsf.org/datarelease/docs/FNIH/OaBioFnihDataOverview.pdf.

Knee MRI acquisition

MRI of both knees was performed on identical 3T systems (Siemens Trio, Erlangen, Germany) at the four OAI clinical sites. MRIs were acquired with a dedicated quadrature transmit/receive knee coil including a coronal intermediate-weighted (IW) two-dimensional (2D) turbo spin-echo, a sagittal three-dimensional (3D) dual echo at steady state (DESS) sequence with additional coronal and axial reformations, and a sagittal IW fat-suppressed turbo spin-echo sequence. Additional parameters of the full OAI pulse sequence protocol and the sequence parameters have been published in detail[9].

Two musculoskeletal radiologists with 18 (FWR) and 21 (AG) years' experience of semi-quantitative assessment of knee OA, blinded to clinical data and case–control status, read the baseline MRIs according to the MRI Osteoarthritis Knee Score (MOAKS) system[10]. The following joint structures were assessed: cartilage morphology, subchondral bone marrow lesions (BMLs), meniscal status, meniscal extrusion, Hoffa-synovitis and effusion-synovitis.

Phenotypic definitions used

Based on semi-quantitative readings knees were stratified according to the following phenotypic definitions as suggested previously[4]: (1) Inflammatory: Maximum grade of Hoffa- or effusion-synovitis 2 or 3 AND sum of both features of 5 or 6 OR Effusion-synovitis being 3 and Hoffa synovitis being 0 or 1; (2) Cartilage/meniscus: Presence of a meniscus score of any type of meniscal substance loss/maceration in the medial and/or lateral compartment and any type of tear in the other compartment, together with presence of ipsi-compartmental cartilage damage grades $\geq$2.1 (in the compartment with substance loss/maceration); (3) Subchondral bone: Maximum subregional BML size of grade 3 in at least one of three knee compartments. Image examples of these phenotypes are presented in Fig. 1. A secondary, less stringent definition for the inflammatory (1) and the cartilage/meniscus phenotype (2) was used for sensitivity analyses: (1) any effusion-synovitis $\geq$ 2; (2) any type of meniscal substance loss/maceration regardless of other compartment AND presence of ipsi-compartmental cartilage damage grades $\geq$ 2.1.

Analytic approach

Knees with KL 1 at baseline were excluded as these are not considered to have radiographic OA in a clinical trial context and would not be typically eligible for trials. Knees with posterior meniscal root tears at baseline were also excluded as these knees are considered at increased risk for structural progression and joint collapse and would therefore not be suitable candidates for clinical trials[11,12]. As the focus of this analysis was structure, our primary outcome was the combined JSL plus composite outcome group (defined as those with JSL only but not pain progression plus those with both JSL and pain progression) with the composite case only group (only those knees with both, pain and structural progression) being the secondary focus. Although DMOAD clinical trials use a combination of structural and clinical outcomes, for comprehensive presentation of the sample and its outcomes we also present the pain outcome only combined with the pain and structural progression outcome. We evaluated the relation of each phenotype (using both definitions, primary and secondary for sensitivity analyses) to odds of being in either the JSL or the composite case progression group compared with those not exhibiting that phenotype using logistic regression. We grouped phenotypes in two ways: first evaluating the odds of progression for those with the phenotype vs without, and then creating a three level grouping of 1) having the phenotype, 2) having a different phenotype, 3) having no phenotype. We ran both unadjusted models and models adjusted for sex, race, and baseline age, BMI, K/L grade, WOMAC pain score, use of pain medication, and JSW. We obtained *P*-values and odds ratios with 95% confidence intervals from the logistic regression models. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC).

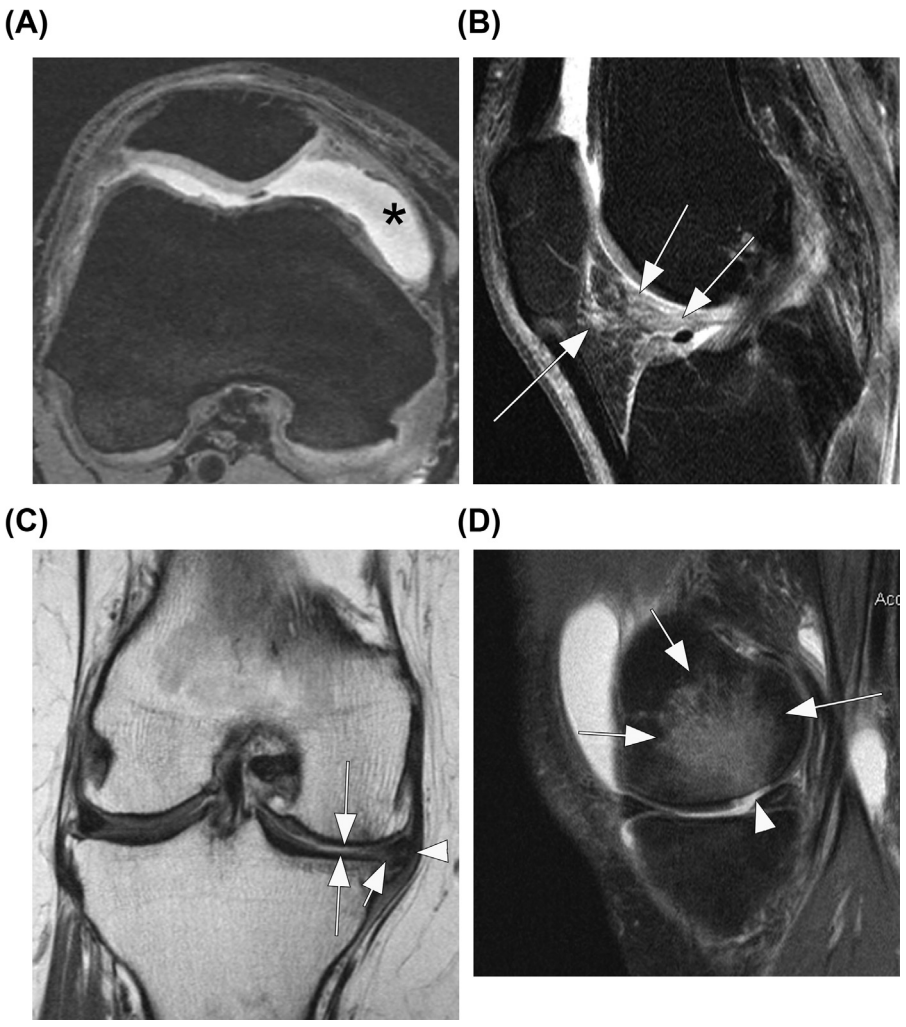

Fig. 1

Image examples of the different structural phenotypes according to the primary definition. A. Inflammatory phenotype. Axial dual echo at steady-state (DESS) MRI shows marked intraarticular joint effusion distending the joint capsule consistent with grade 3 effusion-synovitis according to MOAKS (asterisk). In addition, there is superficial cartilage damage at the medial patella facet. B. Sagittal intermediate-weighted fat-suppressed MRI of the same knee shows diffuse hyperintensity within Hoffa's fat pad (grade 3 according the MOAKS scoring system), a commonly used imaging surrogate on non contrast-enhanced sequences for whole joint synovitis (arrows). The combination of these MRI findings of joint effusion and Hoffa-synovitis fulfills the criteria for the inflammatory phenotype on MRI. C. Cartilage/meniscus phenotye. Coronal intermediate-weighted MRI shows diffuse cartilage loss at the medial femur and corresponding tibia (long arrows). In addition there is substance loss at the free edge of the meniscal body (short arrow) and marked meniscal extrusion beyond the medial joint line (arrowhead). Diffuse meniscal damage predisposes the joint for rapid cartilage loss. In addition, there is a horizontal-oblique tear at the posterior horn of the laterla meniscus (not shown). Findings of bilateral meniscal damage and full thickness cartilage loss fulfill definition of the cartilage/meniscus phenotype.D. Subchondral bone phenotype. Sagittal intermediate-weighted fat-suppressed MRI shows a large (Grade 3) subchondral bone marrow lesion in the medial femur (arrows) characterizing this knee as having the subchondral bone phenotype. In addition there is a focal full thickness cartilage lesion at the central subregion of the medial femur (arrowhead).

Osteoarthritis and Cartilage

Results

After exclusion of KL 1 knees ($n = 71$) and knees with posterior meniscal root tears ($n = 44$), 485 knees were included. Excluded participants were similar to included participants with respect to baseline characteristics and case status (20% of composite cases excluded vs 19% of controls). Mean age of the participants was 61 years (SD ± 8.8), 59 % of the participants were women, average BMI was 31.0 kg/m^2 (SD ± 4.8). 297 knees were KL 2 and 188 knees KL 3. According to the primary definitions, 362 (75%) did not fulfil criteria for any phenotype, while 95 (20%) had the bone phenotype, 22 (5%) the cartilage/meniscus phenotype and 19 (4%) the inflammatory

phenotype. 111 (23%) had one phenotype, 11 (2%) knees had two phenotypes and one knee had three phenotypes. When applying the less stringent secondary definitions these numbers were 274 (56%) not fulfilling definition of any phenotype, 95 (20%) with bone, 104 (21%) with cartilage/meniscus, and 102 (21%) with inflammatory phenotypes. A detailed overview of the phenotypic distribution using both definitions for the included KL 2 and 3 knees is presented in Appendix Ia, while Appendix Ib gives details regarding age, sex and BMI distributions for the different phenotypes.

Results of logistic regression were similar in unadjusted and adjusted models, here we present unadjusted results. Regarding the combined JSL plus composite outcome and the primary phenotype definition, the bone phenotype was associated with a higher odds of the outcome (OR 1.81; [95% CI 1.14, 2.85]) while the inflammatory and cartilage/meniscus phenotypes were not significantly associated with the outcome (OR 0.96 [95% CI 0.38, 2.42] and 1.30 [0.55, 3.07]) compared with those that did not fulfill the definition for that phenotype. Having any one phenotype (vs. none) increased odds for JSL by 1.97 times [95% CI 1.28, 3.05]. Table I provides a detailed overview of these results. Regarding the composite case outcome only and according to the primary phenotype definition, the bone phenotype was also associated with increased odds for having that outcome (i.e., having both structural and pain progression) at follow-up compared with not fulfilling that phenotype definition (OR 1.65, 95% CI [1.04, 2.61]), while the inflammatory and cartilage/meniscus phenotypes were not (OR 1.25, 95% CI [0.48, 3.25] and 0.99, 95% CI [0.40, 2.49]). Having any one phenotype (vs. none) was associated with 1.80 (95% CI1.16, 2.79) times higher odds of experiencing the composite outcome. The detailed composite outcome results for the primary definitions are shown in Appendix II.

In sensitivity analyses using the secondary, less stringent definitions, all phenotypes (vs. none) were associated with an increased risk of JSL, i.e., inflammation OR 1.72, [95% CI 1.10, 2.67], bone OR of 1.81 [95% CI 1.14, 2.85], cartilage/meniscus OR 1.99 [95% CI, 1.27,3.09). Further details regarding JSL as the outcome using the secondary definition are presented in Table II. Regarding the less stringent secondary definitions and the composite outcome, the bone phenotype was associated with increased risk of that outcome (OR 1.65 [95% CI 1.04, 2.61]). The details of this sensitivity analysis (secondary definitions, composite outcome) are shown in Appendix III.

In the additional analyses looking at pain only and pain and structural progression combined as outcomes did not yield significant associations between phenotype and pain case status. These results are presented in Appendix IV.

Discussion

In this cohort of knees defined by specific structural or clinical outcomes, the bone phenotype was associated with an increased odds of having radiographic progression (including those with radiographic progression only and those with both radiographic and pain progression), or having both radiographic and pain

	JSL Case		
	No	Yes	OR (95% CI)
Inflammatory Phenotype			
No	241 (52%)	225 (48%)	REF
Yes	10 (53%)	9 (47%)	0.96 (0.38, 2.42)
Bone Phenotype			
No	213 (55%)	177 (45%)	REF
Yes	38 (40%)	57 (60%)	*1.81 (1.14, 2.85)
Cartilage/meniscus Phenotype			
No	241 (52%)	222 (48%)	REF
Yes	10 (45%)	12 (55%)	1.30 (0.55, 3.07)
Number of Phenotypes			
0	201 (56%)	161 (44%)	REF
1	43 (39%)	68 (61%)	*1.97 (1.28, 3.05)
2+	7 (58%)	5 (42%)	0.89 (0.28, 2.86)
Inflammatory Phenotype Group			
No Phenotype	201 (56%)	161 (44%)	REF
Inflammatory Phenotype	10 (53%)	9 (47%)	1.12 (0.45, 2.83)
Other Phenotype	40 (38%)	64 (62%)	*2.00 (1.28, 3.12)
Bone Phenotype Group			
No Phenotype	201 (56%)	161 (44%)	REF
Bone Phenotype	38 (40%)	57 (60%)	*1.87 (1.18, 2.97)
Other Phenotype	12 (43%)	16 (57%)	1.66 (0.77, 3.62)
Cartilage/meniscus Phenotype Group			
No Phenotype	201 (56%)	161 (44%)	REF
Cartilage/meniscus Phenotype	10 (45%)	12 (55%)	1.50 (0.63, 3.56)
Other Phenotype	40 (40%)	61 (60%)	*1.90 (1.21, 2.98)

*statistically significant at $P < 0.05$.
OR –odds ratio; CI –confidence interval; JSL – joint space loss (i.e., combined JSL plus composite outcome group, defined as those with JSL only but not pain progression plus those with both JSL and pain progression; REF -referent.

Table I Baseline phenotypes and JSL case status (Primary phenotypic definition)

	JSL Case		OR (95% CI)
	No	Yes	
Inflammatory Phenotype (secondary definition)			
No	209 (55%)	174 (45%)	REF
Yes	42 (41%)	60 (59%)	*1.72 (1.10, 2.67)
Bone Phenotype			
No	213 (55%)	177 (45%)	REF
Yes	38 (40%)	57 (60%)	*1.81 (1.14, 2.85)
Cartilage/meniscus Phenotype (secondary definition)			
No	211 (55%)	170 (45%)	REF
Yes	40 (38%)	64 (62%)	*1.99 (1.27, 3.09)
Number of Phenotypes (secondary analysis)			
0	157 (57%)	117 (43%)	REF
1	72 (53%)	64 (47%)	1.19 (0.79, 1.80)
2+	22 (29%)	53 (71%)	*3.23 (1.86, 5.61)
Inflammatory Phenotype Group (secondary definition)			
No Phenotype	157 (57%)	117 (43%)	REF
Inflammatory Phenotype	42 (41%)	60 (59%)	*1.92 (1.21, 3.04)
Other Phenotype	52 (48%)	57 (52%)	1.47 (0.94, 2.30)
Bone Phenotype Group (secondary definition)			
No Phenotype	157 (57%)	117 (43%)	REF
Bone Phenotype	38 (40%)	57 (60%)	*2.01 (1.25, 3.24)
Other Phenotype	56 (48%)	60 (52%)	1.44 (0.93, 2.22)
Cartilage/meniscus Phenotype Group (secondary definition)			
No Phenotype	157 (57%)	117 (43%)	REF
Cart/Meniscus Phenotype	40 (38%)	64 (62%)	*2.15 (1.35, 3.41)
Other Phenotype	54 (50%)	53 (50%)	1.32 (0.84, 2.06)

*statistically significant at $P < 0.05$.
OR –odds ratio; CI –confidence interval; JSL –joint space loss (i.e., combined JSL plus composite outcome group, defined as those with JSL only but not pain progression plus those with both JSL and pain progression; REF –referent.

Table II Baseline phenotypes and JSL case status (Secondary phenotypic definition)

progression together (not including those with only radiographic progression), whereas the inflammatory phenotype or cartilage/meniscus phenotype each individually were not significantly associated with those outcomes. Having any one phenotype (vs. none) also increased the odds of structural and pain progression (i.e., the composite outcome), which was likely largely driven by the bone phenotype given its higher prevalence in this sample. The sensitivity analysis using a less stringent definition for the inflammatory and cartilage/meniscus phenotypes demonstrated that having two phenotypes more than triples odds for having structural progression (only), though this latter group was small and results therefore should be interpreted with caution. Odds for the predefined outcomes increased for the less stringent definitions. Together with higher frequencies of specific phenotypes at baseline using the secondary definitions suggests that these are more useful to be applied in a clinical trial setting, which will also decrease potential screen failures.

It has been suggested previously that there is an urgent medical need to further identify disease phenotypes, preferably by simple technologies, to allow for patient selection of bone, cartilage and inflammation-driven OA phenotypes, and then matching the best intervention to each individual phenotype[5,13]. From a structural MRI-centric perspective, we have suggested previously that it is possible to differentiate five different phenotypes based on the tissue pathologies that are most severely affected by disease with two of them, i.e., the atrophic and hypertrophic ones being rare and of unknown relevance in a clinical trial context[14,15]. For this reason we focused on inflammatory, subchondral bone, and cartilage/meniscus phenotypes only. We clearly acknowledge that this MRI-based attempt has limitations based on the fact that structural phenotypes are likely overlapping, and more than one may be present in an individual[14]. Further, these phenotypes are based on *a priori* hypotheses; whether other relevant structural phenotypes may exist has not been agnostically evaluated. We also acknowledge that structure is only one aspect that drives progression and may define an OA phenotype. In a recent meta-analysis on OA phenotypes Deveza and colleagues found significant heterogeneity across studies in the selection of participants and characteristics and methods used to investigate knee OA phenotypes[2]. Pain sensitization, psychological distress, radiographic severity, BMI, muscle strength, inflammation and comorbidities, also play a part in distinguishing clinically distinct phenotypes. In addition, sex, obesity and other metabolic abnormalities, the pattern of cartilage damage, and inflammation may be implicated in delineating structural knee OA phenotypes. A lack of studies investigating structural phenotypes has been clearly acknowledged[2].

Limitations of our study include the retrospective aspect of our work analyzing a sample that has been defined by certain outcomes nested within the larger OAI study[6]. Future studies will be needed to identify specific patients with a high likelihood of structural progression. In addition we excluded knees with posterior medial root tears as these are commonly considered to be prone to rapid progression and should not be included in clinical trials[11,12]. Also knees without radiographic OA are commonly excluded from clinical trials. We acknowledge that the matching of cases and controls has been broken up by those exclusions but we could also show that KL1 knees and those with posterior root tears were evenly distributed across the different outcome groups and should not have biased our analysis. We did not screen the remaining knees for other diagnoses of exclusion such as subchondral insufficiency fracture, osteonecrosis, recent trauma or malignant bone marrow infiltration as we used available MOAKS readings that were originally performed for the FNIH cohort study. MOAKS does not include these diagnoses. In addition the overall prevalence of phenotypes was low, particularly using the stringent definitions, and additional adapted definitions need to be tested regarding rates of progression and prevalence in a given sample. We have tried this by introducing a secondary, less stringent definition of phenotypes, which resulted in a larger proportion of knees fulfilling these criteria.We further also acknowledge that overlap of phenotypes is not unusual and was observed in 10% of knees using the stringent definitions and 36% of knees using the secondary, less stringent definitions. Whether or not patients or knees fulfilling criteria of a specific phenotype are responsive to a specific therapy or not was not the focus of the current study. Nonetheless, this work supports testing of phenotypes for response to therapy as the next step before considering screening in trials.

The low prevalence of the phenotypes using the primary definitions, particularly the inflammatory and cartilage/meniscus phenotypes (prevalence <5%, $n < 25$), add to the uncertainty around the estimates of association with progression status and make it difficult to draw definitive conclusions about the associations between phenotype and outcome. Future work should evaluate these phenotypes in a larger sample or in a cohort with a higher prevalence of structural deficiencies.

In summary, we demonstrated that the subchondral bone phenotype was associated with an increased risk of radiographic progression, or having both radiographic and pain progression together, whereas the inflammatory phenotype or cartilage/meniscus phenotype each individually were not associated with either outcome. The higher frequencies of specific phenotypes using the secondary definitions suggest that these may be more useful for application in a clinical trial setting, which will result in less screen failures. Phenotypic stratification appears to provide insights into risk for structural or composite structure plus pain progression, and therefore may be useful to consider when selecting patients for inclusion in clinical trials.

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions
Analysis and interpretation of the data: FWR, JEC, TN, MDC, AG.
Drafting of the article: FWR, JEC, TN, MDC, AG.
Provision of study materials or patients: FWR; AG, JEC.
Statistical expertise: JEC, TN.
Obtaining of funding: n/a.
Collection and assembly of data: FWR; AG.
Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; frank.roemer@uk-erlangen.de; froemer@bu.edu).

Funding and role of the funding source
No funding was received for this study. TN was supported by K24 AR070892.

Conflicts of interest
FWR is shareholder of Boston Imaging Core Lab (BICL), LLC. and is consultant to California Institute for Biomedical Research – Calibr.
MDC is shareholder of BICL, LLC.
TN is consultant to Pfizer/Lilly, EMD Merck Serono, Novartis.
JEC is consultant to BICL,LLC.

AG has received consultancies, speaking fees, and/or honoraria from Galapagos, Pfizer/Lilly, Roche, AstraZeneca, Merck Serono, and TissuGene and is President and shareholder of BICL, LLC a company providing image assessment services.

Acknowledgments

We would like to thank the OAI participants, OAI investigators, OAI clinical and technical staff, the OAI coordinating center and the OAI funders for providing this unique public data base. The study and data acquisition was funded by the OAI, a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners of the OAI include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. The sponsors were not involved in the design and conduct of this particular study, in the analysis and interpretation of the data, and in the preparation, review, or approval of the manuscript.

Appendix Ia

KL Grade and Primary Phenotype Definition

	KLG		KL 2 + 3 combined
	2	3	
Inflammatory Phenotype			
No	289 (97%)	177 (94%)	466 (96%)
Yes	8 (3%)	11 (6%)	19 (4%)
Bone Phenotype			
No	244 (82%)	146 (78%)	390 (80%)
Yes	53 (18%)	42 (22%)	95 (20%)
Cartilage/meniscus Phenotype			
No	291 (98%)	172 (91%)	463 (95%)
Yes	6 (2%)	16 (9%)	22 (5%)
Number of Phenotypes			
0	236 (79%)	126 (67%)	362 (75%)
1	55 (19%)	56 (30%)	111 (23%)
2	6 (2%)	5 (3%)	11 (2%)
3	0 (0%)	1 (1%)	1 (0%)
Phenotype			
0 – None	236 (79%)	126 (67%)	362 (75%)
1 – Bone only	47 (16%)	37 (20%)	84 (17%)
1 – Cartilage/meniscus only	6 (2%)	11 (6%)	17 (4%)
1 – Inflammatory only	2 (1%)	8 (4%)	10 (2%)
2 – Bone, Cartilage/meniscus	0 (0%)	3 (2%)	3 (1%)
2 – Bone, Inflammatory	6 (2%)	1 (1%)	7 (1%)
2 – Cartilage/meniscus, Inflammatory	0 (0%)	1 (1%)	1 (0%)
3 – All three phenotypes	0 (0%)	1 (1%)	1 (0%)

KL Grade and Secondary Phenotype Definition

	KLG		KL 2 + 3 combined
	2	3	
Inflammatory Phenotype			
No	241 (81%)	142 (76%)	383 (79%)
Yes	56 (19%)	46 (24%)	102 (21%)
Bone Phenotype			
No	244 (82%)	146 (78%)	390 (80%)
Yes	53 (18%)	42 (22%)	95 (20%)
Cartilage/meniscus Phenotype			
No	282 (95%)	99 (53%)	381 (79%)
Yes	15 (5%)	89 (47%)	104 (21%)
Number of Phenotypes			
0	201 (68%)	73 (39%)	274 (56%)
1	69 (23%)	67 (36%)	136 (28%)
2	26 (9%)	34 (18%)	60 (12%)
3	1 (0%)	14 (7%)	15 (3%)
Phenotype			
0 – None	201 (68%)	73 (39%)	274 (56%)
1 – Bone Only	34 (11%)	10 (5%)	44 (9%)
1 – Cartilage/meniscus only	6 (2%)	44 (23%)	50 (10%)
1 – Infammatory only	29 (10%)	13 (7%)	42 (9%)

(*continued on next page*)

(*continued*)

KL Grade and Secondary Phenotype Definition			
	KLG		KL 2 + 3 combined
	2	3	
2 – Bone, Cartilage/meniscus	0 (0%)	15 (8%)	15 (3%)
2 – Bone, Inflammatory	18 (6%)	3 (2%)	21 (4%)
2 – Cartilage/meniscus, Inflammatory	8 (3%)	16 (9%)	24 (5%)
3 – All three phenotypes	1 (0%)	14 (7%)	15 (3%)

Kellgren–Lawrence grades and distribution of phenotypes (primary and secondary definitions)

Osteoarthritis and Cartilage

Appendix Ib

	Phenotype	
	No	Yes
Inflammatory Phenotype		
Age	61.5 (8.7)	61.1 (10.4)
BMI	31.0 (4.8)	30.6 (4.6)
Gender		
Male	190 (41%)	7 (37%)
Female	276 (59%)	12 (63%)
Bone Phenotype		
Age	61.7 (8.9)	60.4 (8.6)
BMI	30.8 (4.7)	31.9 (5.2)
Gender		
Male	161 (41%)	36 (38%)
Female	229 (59%)	59 (62%)
Cartilage/Meniscus Phenotype		
Age	61.4 (8.7)	62.3 (10.3)
BMI	31.0 (4.8)	31.5 (5.1)
Gender		
Male	184 (40%)	13 (59%)
Female	279 (60%)	9 (41%)
Inflammatory Phenotype (Secondary Definition)		
Age	61.5 (8.5)	61.2 (9.8)
BMI	31.0 (4.8)	31.0 (4.8)
Gender		
Male	148 (39%)	49 (48%)
Female	235 (61%)	53 (52%)
Cartilage/Meniscus Phenotype (Secondary Definition)		
Age	61.2 (8.7)	62.3 (9.1)
BMI	31.1 (4.8)	30.8 (4.8)
Gender		
Male	130 (34%)	67 (64%)
Female	251 (66%)	37 (36%)

Mean (SD) presented for continuous variables. N (%) presented for categorical variables.

Baseline characteristics by baseline phenotype

Osteoarthritis and Cartilage

Appendix II

	Composite JSL + Pain Case		OR (95% CI)
	No	Yes	
Inflammatory Phenotype			
No	318 (68%)	148 (32%)	REF
Yes	12 (63%)	7 (37%)	1.25 (0.48, 3.25)
Bone Phenotype			
No	274 (70%)	116 (30%)	REF
Yes	56 (59%)	39 (41%)	*1.65 (1.04, 2.61)
Cartilage/meniscus Phenotype			
No	315 (68%)	148 (32%)	REF
Yes	15 (68%)	7 (32%)	0.99 (0.40, 2.49)
Number of Phenotypes			
0	257 (71%)	105 (29%)	REF
1	64 (58%)	47 (42%)	*1.80 (1.16, 2.79)
2+	9 (75%)	3 (25%)	0.82 (0.22, 3.07)
Inflammatory Phenotype Group			
No Phenotype	257 (71%)	105 (29%)	REF
Inflammatory Phenotype	12 (63%)	7 (37%)	1.43 (0.55, 3.73)
Other Phenotype	61 (59%)	43 (41%)	*1.73 (1.10, 2.71)
Bone Phenotype Group			
No Phenotype	257 (71%)	105 (29%)	REF
Bone Phenotype	56 (59%)	39 (41%)	*1.70 (1.07, 2.72)
Other Phenotype	17 (61%)	11 (39%)	1.58 (0.72, 3.50)
Cartilage/meniscus Phenotype Group			
No Phenotype	257 (71%)	105 (29%)	REF
Cartilage/Meniscus Phenotype	15 (68%)	7 (32%)	1.14 (0.45, 2.88)
Other Phenotype	58 (57%)	43 (43%)	*1.81 (1.15, 2.86)

*statistically significant at $P < 0.05$.
OR –odds ratio; CI –confidence interval; JSL – joint space loss; REF -referent.

Baseline phenotypes and composite casesStatus (Primary Definition)

Osteoarthritis and Cartilage

Appendix III

	Composite JSL + Pain Case		OR (95% CI)
	No	Yes	
Inflammatory Phenotype (secondary definition)			
No	265 (69%)	118 (31%)	REF
Yes	65 (64%)	37 (36%)	1.28 (0.81, 2.02)
Bone Phenotype			
No	274 (70%)	116 (30%)	REF
Yes	56 (59%)	39 (41%)	*1.65 (1.04, 2.61)
Cartilage/meniscus Phenotype (secondary definition)			
No	264 (69%)	117 (31%)	REF
Yes	66 (63%)	38 (37%)	1.30 (0.82, 2.05)
Number of Phenotypes (secondary definition)			
0	193 (70%)	81 (30%)	REF
1	95 (70%)	41 (30%)	1.03 (0.66, 1.61)
2+	42 (56%)	33 (44%)	*1.87 (1.11, 3.16)
Inflammatory Phenotype Group (secondary definition)			
No Phenotype	193 (70%)	81 (30%)	REF
Inflammatory Phenotype	65 (64%)	37 (36%)	1.36 (0.84, 2.19)
Other Phenotype	72 (66%)	37 (34%)	1.22 (0.76, 1.97)
Bone Phenotype Group (secondary definition)			
No Phenotype	193 (70%)	81 (30%)	REF
Bone Phenotype	56 (59%)	39 (41%)	1.66 (1.02, 2.69)
Other Phenotype	81 (70%)	35 (30%)	1.03 (0.64, 1.65)
Cartilage/meniscus Phenotype Group (secondary definition)			
No Phenotype	193 (70%)	81 (30%)	REF
Cartilage/meniscus Phenotype	66 (63%)	38 (37%)	1.37 (0.85, 2.21)
Other Phenotype	71 (66%)	36 (34%)	1.21 (0.75, 1.95)

*statistically significant at $P < 0.05$.
OR –odds ratio; CI –confidence interval; JSL – joint space loss; REF -referent.

Baseline phenotypes and composite case status (Secondary Definition)

Osteoarthritis and Cartilage

Appendix IVa

	Pain Case*		OR (95% CI)
	No	Yes	
Inflammatory Phenotype			
No	232 (50%)	234 (50%)	REF
Yes	8 (42%)	11 (58%)	1.36 (0.54, 3.45)
Bone Phenotype			
No	199 (51%)	191 (49%)	REF
Yes	41 (43%)	54 (57%)	1.37 (0.87, 2.16)
Cartilage/meniscus Phenotype			
No	227 (49%)	236 (51%)	REF
Yes	13 (59%)	9 (41%)	0.67 (0.28, 1.59)
Number of Phenotypes			
0	184 (51%)	178 (49%)	REF
1	50 (45%)	61 (55%)	1.26 (0.82, 1.93)
2+	6 (50%)	6 (50%)	1.03 (0.33, 3.27)
Inflammatory Phenotype Group			
No Phenotype	184 (51%)	178 (49%)	REF
Inflammatory Phenotype	8 (42%)	11 (58%)	1.42 (0.56, 3.62)
Other Phenotype	48 (46%)	56 (54%)	1.21 (0.78, 1.87)
Bone Phenotype Group			
No Phenotype	184 (51%)	178 (49%)	REF
Bone Phenotype	41 (43%)	54 (57%)	1.36 (0.86, 2.15)
Other Phenotype	15 (54%)	13 (46%)	0.90 (0.41, 1.94)
Cartilage/meniscus Phenotype Group			
No Phenotype	184 (51%)	178 (49%)	REF
Cartilage/meniscus Phenotype	13 (59%)	9 (41%)	0.72 (0.30, 1.72)
Other Phenotype	43 (43%)	58 (57%)	1.39 (0.89, 2.18)

* pain only and pain and structural progression combined.
OR –odds ratio; CI –confidence interval; REF -referent.

Baseline phenotypes and pain case status (Primary Definition)

Osteoarthritis and Cartilage

Appendix IVb

	Pain Case*		OR (95% CI)
	No	Yes	
Inflammatory Phenotype (secondary definition)			
No	191 (50%)	192 (50%)	REF
Yes	49 (48%)	53 (52%)	1.08 (0.70, 1.67)
Bone Phenotype			
No	199 (51%)	191 (49%)	REF
Yes	41 (43%)	54 (57%)	1.37 (0.87, 2.16)
Cartilage/meniscus Phenotype (secondary definition)			
No	183 (48%)	198 (52%)	REF
Yes	57 (55%)	47 (45%)	0.76 (0.49, 1.18)
Number of Phenotypes (secondary analysis)			
0	135 (49%)	139 (51%)	REF
1	68 (50%)	68 (50%)	0.97 (0.64, 1.47)
2+	37 (49%)	38 (51%)	1.00 (0.60, 1.66)
Inflammatory Phenotype Group (secondary definition)			
No Phenotype	135 (49%)	139 (51%)	REF
Inflammatory Pheno	49 (48%)	53 (52%)	1.05 (0.67, 1.66)
Other Phenotype	56 (51%)	53 (49%)	0.92 (0.59, 1.43)
Bone Phenotype Group (secondary definition)			
No Phenotype	135 (49%)	139 (51%)	REF
Bone Phenotype	41 (43%)	54 (57%)	1.28 (0.80, 2.05)
Other Phenotype	64 (55%)	52 (45%)	0.79 (0.51, 1.22)
Cartilage/meniscus Phenotype Group (secondary definition)			
No Phenotype	135 (49%)	139 (51%)	REF
Cart/Meniscus Phenotype	57 (55%)	47 (45%)	0.80 (0.51, 1.26)
Other Phenotype	48 (45%)	59 (55%)	1.19 (0.76, 1.87)

* pain only and pain and structural progression combined.
OR –odds ratio; CI –confidence interval; REF -referent.

Baseline phenotypes and pain case status (Secondary Definition)

Osteoarthritis and Cartilage

References

1. Hunter DJ, Altman RD, Cicuttini F, Crema MD, Duryea J, Eckstein F, *et al.* OARSI Clinical Trials Recommendations: knee imaging in clinical trials in osteoarthritis. Osteoarthritis Cartilage 2015;23:698–715.
2. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage 2017;25:1926–41.
3. Oo WM, Yu SP, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs 2018;23:331–47.
4. Roemer FW, Collins J, Kwoh CK, Hannon MJ, Neogi T, Felson DT, *et al.* MRI-based screening for structural definition of eligibility in clinical DMOAD trials: rapid OsteoArthritis MRI Eligibility Score (ROAMES). Osteoarthritis Cartilage 2020;28(1):71–81.
5. Karsdal MA, Bihlet A, Byrjalsen I, Alexandersen P, Ladel C, Michaels M, *et al.* OA phenotypes, rather than disease stage, drive structural progression–identification of structural progressors from 2 phase III randomized clinical studies with symptomatic knee OA. Osteoarthritis Cartilage 2015;23:550–8.
6. Collins JE, Losina E, Nevitt MC, Roemer FW, Guermazi A, Lynch JA, *et al.* Semiquantitative imaging Biomarkers of knee osteoarthritis progression: data from the foundation for the National Institutes of health osteoarthritis Biomarkers Consortium. Arthritis Rheumatol 2016;68:2422–31.
7. Nevitt MC, Felson DT, Lester G. The Osteoarthritis Initiative: protocol for the cohort study. URL: http://oaiepi-ucsforg/datarelease/docs/StudyDesignProtocol.pdf p. 19–20.
8. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45:384–91.
9. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433–41.
10. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Congahan PG, Boudreau RM, *et al.* Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19:990–1002.
11. Guermazi A, Hayashi D, Jarraya M, Roemer FW, Zhang Y, Niu J, *et al.* Medial posterior meniscal root tears are associated with development or worsening of medial tibiofemoral cartilage damage: the multicenter osteoarthritis study. Radiology 2013;268:814–21.
12. LaPrade CM, Foad A, Smith SD, Turnbull TL, Dornan GJ, Engebretsen L, *et al.* Biomechanical consequences of a nonanatomic posterior medial meniscal root repair. Am J Sports Med 2015;43:912–20.
13. Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis–a case for personalized health care? Osteoarthritis Cartilage 2014;22:7–16.
14. Roemer FW, Kwoh CK, Hayashi D, Felson DT, Guermazi A. The role of radiography and MRI for eligibility assessment in DMOAD trials of knee OA. Nat Rev Rheumatol 2018;14:372–80.
15. Crema MD, Felson DT, Guermazi A, Nevitt MC, Niu J, Lynch JA, *et al.* Is the atrophic phenotype of tibiofemoral osteoarthritis associated with faster progression of disease? The MOST study. Osteoarthritis Cartilage 2017;25:1647–53.